

Rapid relief of block by mecamlamine of neuronal nicotinic acetylcholine receptors of rat chromaffin cells in vitro: An electrophysiological and modeling study

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Abstract

The mechanism responsible for the blocking action of mecamlamine on neuronal nicotinic acetylcholine receptors (nAChRs) was studied on rat isolated chromaffin cells recorded under whole-cell patch clamp. Mecamlamine strongly depressed ($IC_{50} = 0.34 \mu M$) inward currents elicited by short pulses of nicotine, an effect slowly reversible on wash. The mecamlamine block was voltage-dependent and promptly relieved by a protocol combining membrane depolarization with a nicotine pulse. Either depolarization or nicotine pulses were insufficient per se to elicit block relief. Block relief was transient; response depression returned in a use-dependent manner. Exposure to mecamlamine failed to block nAChRs if they were not activated by nicotine or if they were activated at positive membrane potentials. These data suggest that mecamlamine could not interact with receptors either at rest or at depolarized level. Other nicotinic antagonists like dihydro- β -erythroidine or tubocurarine did not share this action of mecamlamine although proadifen partly mimicked it. Mecamlamine is suggested to penetrate and block open nAChRs that would subsequently close and trap this antagonist. Computer modeling indicated that the mechanism of mecamlamine blocking action could be described by assuming that 1) mecamlamine-blocked receptors possessed a much slower, voltage-dependent isomerization rate, 2) the rate constant for mecamlamine unbinding was large and poorly voltage dependent. Hence, channel reopening plus depolarization allowed mecamlamine escape and block relief. In the presence of mecamlamine, therefore, nAChRs acquire the new property of operating as coincidence detectors for concomitant changes in membrane potential and receptor occupancy.
